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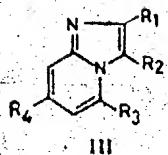
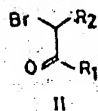
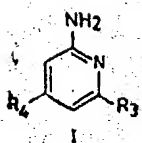
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## INDIAN PATENT SPECIFICATION

<p>(51) Int. Cl.<sup>1</sup> : C 07 D 47/04 A 61 K 31/44</p> <p>(52) Ind. Cl. : 32 F-1 55 E-4</p>	A	<p>(11) Document No. 179788 IN</p> <p>Date of Document : 10.02.92</p> <p>(42) Date of Publication : 06-12-97</p>
<p>(21) Application No. : 102 DEL 92</p> <p>(22) Date of filing: 10.02.92</p> <p>Claims : 3</p> <p>Text : Pages; Orgs. Sheets. 8 1</p>	<p>(71) Applicant : COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH, Rafi Marg, New Delhi-110001, India, an Indian registered body incorporated under the Registration of Societies Act (Act XXI of 1860).</p> <p>(72) Inventor : KANWAL RAJ, INDIAN SURENDRA PAL VISHNOI, INDIA ABOO SHOEIB, INDIA DEOKI NANDAN GUPTA, INDIA GOVIND KESHRI, INDIA VEL PRAKASH KAMBOJ, INDIA</p> <p>(73) Agent :</p> <p>Examiner : HARDEV KARAR</p>	

(54) Title : A PROCESS FOR THE PREPARATION OF NOVEL 2-SUBSTITUTED AND 2,5,7-TRI-SUBSTITUTED IMIDAZO-(1,2-a)PYRIDINES SHOWING ANTIFERTILITY ACTIVITY.

(57) Abstract: A process for the preparation of novel 2-substituted and 2,5,7 trisubstituted imidazo (1,2-a) pyridines of the formula III, where  $R_1$  represents substituted phenol such as halophenyl preferably chloro or bromo phenyl, methyl phenyl, nitro phenyl, hydroxy phenyl, methoxy phenyl, ethoxy phenyl or carboxymethyl & carbethoxymethyl;  $R_2=H$ ;  $R_3=R_4=H$  or  $CH_3$ , which comprises refluxing correspondingly substituted 2-aminopyridines of formula I where  $R_3$  &  $R_4$  represent hydrogen or methyl groups with correspondingly



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substituted - bromoketone of the formula II where  $R_1$  represents substituted phenol such as halophenyl preferably chloro or bromophenyl, alkyl phenyl, nitro phenyl, hydroxy phenyl, methoxy phenyl, ethoxy phenyl or carboxymethyl & carbethoxymethyl ;  $R_2=H$ ; in the presence of an aprotic solvent for a period ranging from 2-24 hrs. at a temperature in the range  $36^{\circ}$ - $90^{\circ}$ C and recovering the 2-substituted and 2,5,7 trisubstituted imidazo (1,2-a) pyridines, of formula III by conventional methods.

This invention relates to a process for the preparation of novel 2-substituted and 2,5,7 trisubstituted imidazo-(1,2-a) pyridines.

The novel 2-substituted and 2,5,7 trisubstituted imidazo-(1,2-a) pyridines prepared by the process of present invention have the formula III shown in the drawing accompanying this specification where  $R_1$  represents substituted phenyl such as halophenyl, preferably chloro or bromo phenyl, methyl phenyl, nitro phenyl hydroxy phenyl, methoxy phenyl, ethoxyphenyl, carboxymethyl & carbethoxymethyl;  $R_2 = H$ ;

$R_3 = R_4 = H$  or  $CH_3$

The compounds of the formula III prepared by the process of the present invention found to be useful as antiimplantation abortifacient agents. These compounds when tested in hamster for antifertility activity showed 30-100% protection against pregnancy at 2.5 - 20 mg / kg by oral and subcutaneous routes.

Accordingly, the present invention provides a process for the preparation of novel 2-substituted and 2,5,7 trisubstituted imidazo (1,2-a) pyridines of the formula III shown in the drawing accompanying this specification, where  $R_1$  represents substituted phenol such such as halophenyl preferably chloro or

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bromo phenyl, methyl phenyl, nitro phenyl, hydroxy phenyl, methoxy phenyl, ethoxy phenyl or carboxymethyl & carbethoxymethyl;  $R_2 = H$ ;  $R_3 = R_4 = H$  or  $CH_3$ ,

which comprises refluxing correspondingly substituted 2-aminopyridines of formula I where  $R_3$  &  $R_4$

represent hydrogen or methyl groups with correspondingly substituted - bromoketone of the formula II where  $R_1$  represents substituted phenol such as halo-

phenyl preferably chloro or bromophenyl, alkyl phenyl, nitro phenyl, hydroxy phenyl, methoxy phenyl, ethoxy phenyl or carboxymethyl & carbethoxymethyl ;

$R_2 = H$ ; in the presence of an aprotic solvent for a

period ranging from 2-24 hrs. at a temperature in the range  $36-90^\circ C$  and recovering the 2-substituted and 2,5,7 trisubstituted imidazo (1,2-a) pyridines, of formula III by conventional methods.

In a preferred embodiment of the invention the solvent used may be selected from chloroform dichloromethane, benzene THF and the like.

The compounds of the formula III prepared by the process of the invention,

where  $R_1$  represents  $2 / 3 / 4 - OHC H$  and

$R_2, R_3$  &  $R_4$  represent hydrogen are also

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useful for the preparation of compounds of the formula IV i.e. the corresponding ethers of the formula III by treating with appropriate halides.

This process has been made subject matter of the copending application No. 104/DEL/92

In yet another pending co-application <sup>No. 103/DEL/92</sup> we have described a process for the preparation of compounds of the formula V where R<sub>1</sub> represents bromophenyl (4-Br-C<sub>6</sub>H<sub>4</sub>), R<sub>2</sub> represents diethylaminomethyl, cyclic amino methyl; R<sub>3</sub> & R<sub>4</sub> represents hydrogen, starting from the compounds of the formula III, prepared by the process of the present invention. Compounds of the formula IV & V possess antifertility activity.

The invention is further illustrated by the examples given below which should not, however, be construed to limit the scope of the present invention.

#### EXAMPLE 1

2-(4-hydroxyphenyl)imidazo[1,2-a]pyridine hydrobromide of formula III where R<sub>1</sub> represents 4-hydroxyphenyl, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> represent Hydrogen

A solution of 4-hydroxyphenacyl bromide (215 mg, 1 mmol) and 2-aminopyridine (94 mg, 1 mmol) in chloroform (10 ml) was refluxed at 95° for 10 hr. On removal

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of the solvent, the residue was heated at the same temperature for 0.5 hr. and crystallised from a mixture of  $\text{CH}_3\text{OH}/\text{CHCl}_3$ . The title compound, 210 mg, m.p.  $231-32^\circ\text{C}$  was obtained in 72% yield.

#### EXAMPLE 2

2-(4-Bromophenyl)-5,7-dimethylimidazo-[1,2-a]pyridine hydrobromide of formula III where  $R_1$  represents 4-Bromophenyl,  $R_2$ , Hydrogen,  $R_3$  &  $R_4$  methyl

A solution of 4-bromophenacyl bromide (278 mg, 1 mmol) and 2-amino-4,6-dimethyl pyridine (122 mg, 1 mmol) was refluxed in chloroform (20 ml) at  $80^\circ\text{C}$  for 20 hr. On removal of the solvent, the residue was heated at the same temperature under vacuo for 1/2 hr. and crystallised from MeOH/ether. The title compound, m.p.  $168-69^\circ$ , was isolated in 50% yield.

#### EXAMPLE-3

2-(2-Hydroxyphenyl)imidazo[1,2-a]pyridine hydrobromide of formula III where  $R_1$  represents 2-hydroxyphenyl,  $R_2, R_3, R_4$  represent hydrogen

A solution of 2-hydroxyphenacyl bromide (215 mg, 1 mmol), 2-aminopyridine (94 mg, 1 mmol) was refluxed in chloroform for 24 hr. The residue obtained after removal

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of solvent was crystallised from ethanol, m.p. 241-243°. The title compound was obtained in 50% yield.

#### EXAMPLE-4

2-(2-Hydroxyphenyl)-imidazo[1,2-a]pyridine hydrobromide of formula III where  $R_1$  represents 2-hydroxyphenyl;  $R_2, R_3, R_4$  represent hydrogen

A solution of 2-hydroxyphenacyl bromide (215 mg, 1 mmol), 2-aminopyridine (94 mg, 1 mmol) was refluxed in methylene chloride (30 ml) at 50° for 10 hr. After removal of the solvent, the residue was crystallised from ethanol/ether, m.p. 241-43°. The title compound was obtained in 40% yield.

#### EXAMPLE-5

2-Carbethoxymethyl-imidazo[1,2-a]pyridine of formula III, where  $R_1$  represents carbethoxymethyl-;  $R_2, R_3, R_4$  represent hydrogen

A mixture of 2-aminopyridine (2.82 g; 0.03 mol) and 4-bromo-3-oxo-butanoic acid ethyl ester (6.27 g; 0.03 mol) was refluxed in  $\text{CHCl}_3$  (50 ml) for 3 hr. On removal of the solvent, the residue was heated at 100°C for 1 hr, neutralized with  $\text{NH}_4\text{OH}$ , extracted with  $\text{CHCl}_3$  and dried ( $\text{Na}_2\text{SO}_4$ ). The solvent removed and the residue purified on Si-gel column using 2% methanol in  $\text{CHCl}_3$  (V/V). The title compound (2.4 g) was obtained as a semi-solid mass in 40% yield.

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WE CLAIM:-

1. A process for the preparation of novel 2-substituted and 2,5,7 trisubstituted imidazo (1,2-a) pyridines of the formula III shown in the drawing accompanying this specification, where R represents

substituted phenol such such as halophenyl preferably chloro or bromo phenyl, methyl phenyl, nitro phenyl, hydroxy phenyl, methoxy phenyl, ethoxy phenyl or carboxymethyl & carbethoxymethyl;  $R_1 = H$ ;  $R_2 = R_3 = R_4 = H$

or  $CH_3$ , which comprises refluxing correspond-

ingly substituted 2-aminopyridines of formula I where  $R_3$  &  $R_4$  represent hydrogen or methyl groups with

correspondingly substituted - bromoketone of the formula II where  $R_1$  represents substituted phenol

such as halophenyl preferably chloro or bromophenyl, alkyl phenyl, nitro phenyl, hydroxy phenyl, methoxy phenyl, ethoxy phenyl or carboxymethyl & carbethoxymethyl;  $R_2 = H$ ; in the presence of an aprotic solvent

for a period ranging from 2-24 hrs. at a temperature in the range 36<sup>0</sup> -90<sup>0</sup> C and recovering the 2-substituted and 2,5,7 trisubstituted imidazo (1,2-a) pyridines, of formula III by conventional methods.

2. A process as claimed in claim 1 wherein solvent used is selected from chloroform, dichloromethane, benzene, THF.



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3. A process for the preparation of novel 2-substituted and 2,5,7 tri substituted imidazo (1,2-a) pyridines of the formula III as defined in the claim 1 substantially as herein described with reference to the examples.

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Dated this 10 day of Feb., 1992

*Balashmi*

( Mrs. L. Balasubrahmanyam )

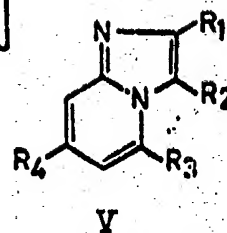
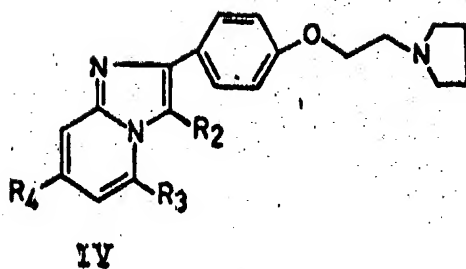
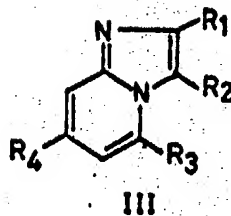
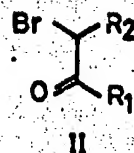
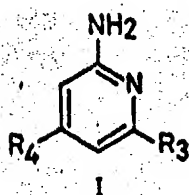
Scientist (Patents)

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*N. R. Srinivasan*

(APPLICANTS)